STATISTICAL ANALYSIS PLAN	
Study Code	D8850C00002
Edition Number	V4.0
Date	29-Jul-2021

A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19

Study Statistician: PPD

Global Product Statistician: PPD

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	09Dec2020	PPD	Not Applicable – first version based on CSP v3
2.0	14Apr2021	PPD	Updates reflect CSP changes in versions 4, 5, 6, and 7. Key changes include: Addition of unblinding for proper consideration of COVID-19 vaccine as an intercurrent event, revised definitions for intercurrent events, primary endpoint definition, changes in primary estimand, timing of the primary analysis, removal of the interim analysis, added subgroups, increase of sample size for clonal material, last visit of Day 457 added, addition of key supportive analysis, removal of BSSR, proportions of cohorts to be recruited, removal of strata caps within cohorts, simplification of supplementary analyses, removal of select lab summaries, removal of IQVIA as Analysis & Reporting vendor.
3.0	30Jun2021	PPD	Updates reflect CSP changes in version 8. Key changes include: Additional estimand of the primary endpoint and inclusion in the multiple testing hierarchy. Day 366 endpoint changed from Key Secondary to Exploratory, and nucleocapsid antibodies endpoint from Secondary to Key Secondary. Other updates include: Addition of imputation rules for partial COVID-19 vaccination dates. Removal of Symptomatic COVID-19 Analysis Set. Revision of analysis method to be used if convergence cannot be achieved using primary analysis method.
4.0	23Jul2021	PPD	Updates reflect CSP changes in version 9. Editorial changes are not listed. Key changes

			include: Removal of "to properly consider vaccination for COVID-19" with respect to unblinded intercurrent event language. Addition of Morbidity Adjudication Committee. Removal of vaccine efficacy censor estimand. Addition of key supportive estimand including death due to any cause. Revision of multiple testing hierarchy. Change from age at randomization to age at informed consent. Removal of "severe" requirement for COVID-19 hospitalizations to be included in primary endpoint. Revision to sensitivity analysis approach. Addition of descriptive statistics for Day 366 exploratory endpoint.

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol D8850C00002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 9.0, dated 26Jul2021.

The term IMP (investigational medicinal product) is used throughout this SAP to include both treatment groups (AZD7442 and placebo). AZD7442 is specified when referring only to those who received active intervention.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To estimate the efficacy of a single intramuscular (IM) dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183
- To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo

2.2. SECONDARY OBJECTIVES

The key secondary objective is:

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection

The other secondary objectives are:

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19
- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits
- To assess the pharmacokinetics (PK) of AZD7442 administered as a single dose of 300 mg IM
- To evaluate anti-drug antibody (ADA) responses to AZD7442 in serum

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366
- To evaluate the single dose pharmacokinetic concentrations of AZD7442 in nasal fluid
- To determine anti-SARS-CoV-2 neutralizing antibody (nAb) levels in serum following a single IM dose of AZD7442 or placebo
- To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To characterize resistance to AZD7442 (Illness Visits) – not covered by this SAP
- To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)
- To assess additional immune responses following a single IM dose of AZD7442 or placebo – not covered by this SAP

2.4. ESTIMANDS

Table A: List of Estimands – Primary

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Primary Efficacy Estimand – The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183.	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
Primary Safety	Safety analysis set, defined as all participants who received at least one of the planned	Single dose of AZD7442 (× 2 IM	Incidence of adverse	Not Applicable	Descriptive statistics, including

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Estimand – The safety and tolerability of a single IM dose of AZD7442 compared to placebo	injections of IMP. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	injections, 1 for each mAb component) or placebo	events, serious adverse events, medically attended adverse events, and adverse events of special interest post dose of IMP		number and percentages of participants who have the incidence; Number of the events.

Table B: List of Estimands – Key Secondary

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Key Secondary Estimand – The efficacy	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or	The incidence of participants who have a	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	placebo	post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.	other COVID-19 preventive product, in both cases prior to having met the criteria for the key secondary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).	incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

Table C: List of Estimands – Other Secondary

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of	Full pre-exposure analysis set, defined as all participants who were randomized, received at least of the planned injections of IMP, and did	Single dose of AZD7442 (× 2 IM injections, 1 for each	The incidence of SARS-CoV-2 RT-	Participants who become unblinded to treatment assignment	Prophylactic efficacy, calculated as 1-relative risk.

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	mAb component) or placebo	PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.	and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for this secondary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).	(Relative risk is the incidence of severe or critical symptomatic infection in the AZD7442 group relative to the incidence of severe or critical symptomatic infection in the control group.)
The efficacy of a single IM dose of AZD7442 compared to placebo for the	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics:	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of COVID-19-related Emergency Department visits occurring after	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of COVID-19-related emergency

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
prevention of COVID-19-related Emergency Department visits	Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.		dosing with IMP.	prior to having met the criteria for this secondary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).	department visits in the AZD7442 group relative to the incidence of COVID-19-related emergency department visits in the control group.)
The pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM	Pharmacokinetic analysis set, defined as all participants who receive at least one of the planned injections of AZD7442, from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum PK observation post dose. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component)	Serum AZD7442 concentrations. PK parameters if data permit.	Not Applicable	Individual AZD7442 (AZD8895 and AZD1061) serum concentration data descriptive statistics; Pharmacokinetic exposure (i.e., AUCs) and other PK parameters may

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
	inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.				be estimated using non compartmental analysis, if data permit.
ADA responses to AZD7442 in serum	ADA analysis set, defined as all participants who received at least one of the planned injections of IMP and who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Incidence of ADA to AZD7442 in serum.	Not Applicable	Descriptive statistics, including number and percentage of participants who developed ADAs to AZD7442.

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
	and COVID-19.				

Table D: List of Estimands – Exploratory

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of the first case of SARS-CoV-2 RT PCR positive symptomatic illness occurring after dosing with IMP through Day 366.	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for this exploratory efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
	and COVID-19.			handled using a while on treatment strategy).	
The single dose pharmacokinetic concentrations of AZD7442 in nasal fluid	A subset of the pharmacokinetic analysis set, per available data, defined as all participants who receive at least one of the planned injections of AZD7442, from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum PK observation post dose. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component)	AZD7442 nasal concentrations.	Not Applicable	Individual concentration data with descriptive statistics
Anti-SARS-CoV-2 nAb	The nAb analysis set, defined as all participants who received at least one of the planned	Single dose of AZD7442 (× 2 IM	Post-treatment	Not Applicable	GMT and GMFR with descriptive

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
levels in serum following a single IM dose of AZD7442 or placebo	injections of IMP, from whom blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum titer observation post dose. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	injections, 1 for each mAb component) or placebo	GMTs and GMFRs from baseline value through Day 457 after single IM dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo neutralizatio n assay).		statistics
SARS-CoV-2 viral loads in infected participants treated with a single IM	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, and who met the criteria for symptomatic COVID-19 and	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Viral genome copies in NP swabs collected at Illness Visits	Not Applicable	Observed and change from baseline descriptive statistics

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
dose of AZD7442 or placebo (Illness Visits)	began Illness Visits following confirmed SARS-CoV-2 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.		as determined by qRT-PCR.		
Duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, and who met the criteria for symptomatic COVID-19 and began Illness Visits following confirmed SARS-CoV-2 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Duration of SARS-CoV-2 shedding in saliva over time.	Not Applicable	Descriptive statistics on number of days of shedding

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
AZD7442 or placebo (Illness Visits)	benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.				
Symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, and who met the criteria for symptomatic COVID-19 and began Illness Visits following confirmed SARS-CoV-2 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28.	Not Applicable	Descriptive statistics, including number and percentage of participants with symptoms.

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
	intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.				

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, randomized, double-blind, placebo-controlled, multi-country, multi-center study assessing the safety and efficacy of a single dose of AZD7442 (× 2 IM injections) compared to placebo for the prevention of COVID-19.

Participants will be adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. Participants will be enrolled into one of two cohorts:

- Cohort 1: Adults ≥ 60 years of age. All participants will be considered as being at increased risk for inadequate response to active immunization on the basis of age (presumed immunosenescence). Cohort 1 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by residence in a long-term care facility or not.
- Cohort 2: Adults < 60 years of age. Cohort 2 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by risk of exposure to infection with SARS-CoV-2.

Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single dose (× 2 IM injections) of either 300 mg of AZD7442 (n = approximately 3433) or saline placebo (n = approximately 1717) on Day 1. Enrollment will occur in two stages, which is contingent upon evaluation of 7-day safety data of Stage 1 enrollment by an independent DSMB and its recommendation to proceed with Stage 2:

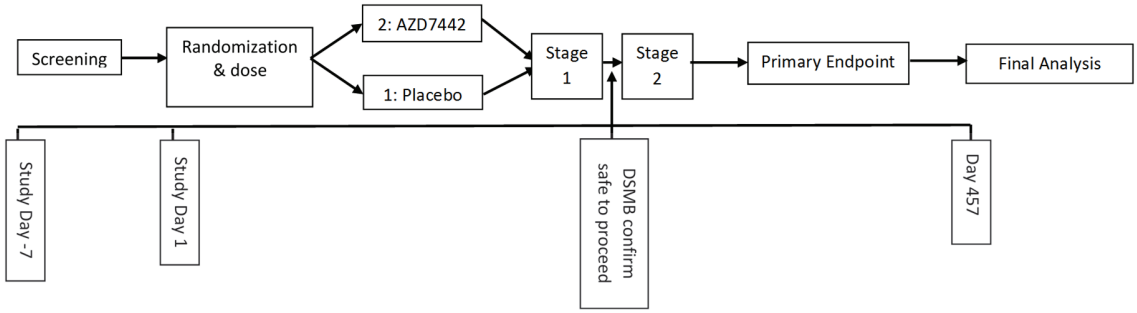
- Stage 1 (N = 300 [at least 150 from Cohort 1]: 200 to AZD7442, 100 to placebo). The first 15 participants (Sentinel Cohort), will undergo safety monitoring for 4 hours post IMP administration before dosing the rest of the participants in Stage 1. The remaining 285 participants will undergo safety monitoring for 2 hours post IMP administration.

- Stage 2 (N = 4850: 3233 to AZD7442, 1617 to placebo). Stage 2 will start only after an independent Data Safety Monitoring Board (DSMB) has confirmed it is appropriate to proceed. The DSMB will evaluate 7-day safety data from participants dosed in Stage 1. If hypersensitivity reactions are observed during Stage 1, safety monitoring for 2 hours post IMP administration will be implemented for Stage 2; otherwise the minimum safety monitoring time will be 1 hour.

To allow for the assessment of clonal material, 150 participants in the US will receive the clonal material or placebo in a 2:1 ratio. The participants will be recruited according to the current inclusion and exclusion criteria and will be followed as per the schedule of activities. A PK analysis will be performed of pooled versus clonal material.

Following a screening period of ≤ 7 days, participants will receive a single dose (× 2 IM injections) of IMP. After administration of the dose of IMP on Day 1, participants will undergo follow-up for 15 months (until Day 457).

Figure A: Study Design



Following screening (-7 to 0 days), randomization will occur in 2 stages and is contingent on safety. The planned primary analysis will occur after approximately 24 primary endpoint events have occurred or 30% of study participants have become unblinded, whichever occurs first. A final analysis is planned when all participants complete the study (Day 457).
DSMB, Data Safety Monitoring Board

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

3.3. CHANGES TO ANALYSES FROM PROTOCOL

There are no changes to the analyses planned in the protocol.

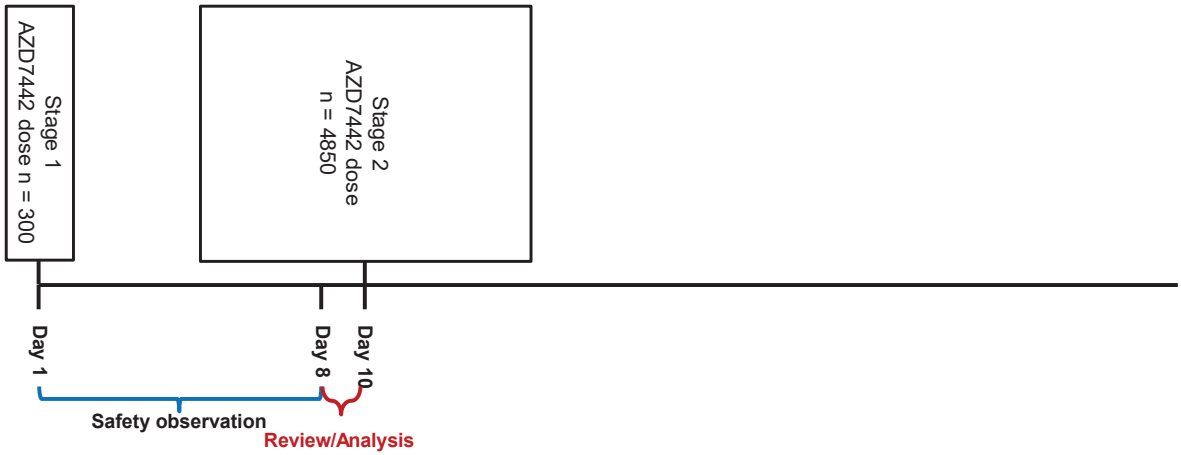
4. PLANNED ANALYSES

4.1. DATA AND SAFETY MONITORING BOARD (DSMB)

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study.

The DSMB will meet monthly and make any necessary recommendations to the Sponsor based on their evaluations of emerging data. In particular, the evaluation of 7-day safety data from participants dosed in Stage 1 will be performed by the DSMB, who will advise the sponsor on whether it is appropriate to proceed into Stage 2 of the study. The DSMB will also review study progress and monitor for evidence of harm resulting from AZD7442. If required, the DSMB will recommend temporarily stopping or termination of the study. There is no formal efficacy look by the DSMB with the potential for early stopping due to efficacy planned for this study.

Figure B: Study Dose Exposure Expansion



Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

4.2. MORBIDITY ADJUDICATION COMMITTEE

An independent Morbidity Adjudication Committee (MAC) will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to evaluate whether the causes of death for participants are considered COVID-19 associated. Only adjudicated deaths will be included in efficacy endpoints. All fatal events will be further assessed as part of safety evaluation. Further details of this adjudication will be provided in a separate Morbidity Adjudication Committee Charter.

4.3. INTERIM ANALYSIS

No interim analysis is planned.

4.4. PRIMARY ANALYSIS

The primary analysis will occur after approximately 24 primary endpoint events have been confirmed across the active and control groups or 30% of study participants have become unblinded (at which point the ability to observe primary endpoint events is expected to have diminished), whichever occurs earlier. All primary endpoint events accrued up until the data cut-off (DCO) will be included in the primary analysis. The date for the DCO for this analysis will be the date that the 24th primary endpoint event is confirmed or the date that 30% of study participants have become unblinded, whichever occurs earlier.

All planned primary analyses are detailed in this SAP and will be performed by AstraZeneca or its delegates following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, database lock (DBL), and

analysis team unblinding. The primary analysis will be carried out by an unblinded analysis team, and the procedure will be detailed in an unblinding plan; participant level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented.

4.5. FINAL ANALYSIS

The final analysis will be conducted at the end of the study, i.e., after the last participant dosed has completed the Day 457 visit.

All final, planned analyses are detailed in this SAP and will be performed by AstraZeneca or its delegates following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, DBL, and general study unblinding.

5. ANALYSIS SETS

5.1. ALL PARTICIPANTS ANALYSIS SET

The all participants analysis set (PAS) will contain all participants screened for the study. All participants analysis set is to be used for reporting disposition and screening failures.

All participants screened are those who provide informed consent.

5.2. FULL ANALYSIS SET

The Full Analysis Set (FAS) will contain all participants in the PAS who were randomized and received at least one of the planned injections of IMP, irrespective of their protocol adherence and continued participation in the study. Per the protocol a dose is two injections, but any participant receiving at least one injection will be included in the FAS based on intent-to-treat (ITT) principle. Participants will be analyzed according to their randomized treatment irrespective of whether they have prematurely discontinued, according to the ITT principle. Participants who withdraw consent to participate in the study will be included up to the date of their study termination.

For analyses and displays based on the FAS, participants will be classified according to randomized treatment regardless of what treatment they actually received.

5.3. FULL PRE-EXPOSURE ANALYSIS SET

The Full Pre-Exposure Analysis Set (FPAS) will contain all participants in the FAS who did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection.

For analyses and displays based on the FPAS, participants will be classified according to randomized treatment regardless of what treatment they actually received.

5.4. SAFETY ANALYSIS SET

The safety analysis set (SAF) will contain all participants in the PAS who received at least one of the planned injections of IMP. Per the protocol a dose is two injections, but any participant receiving at least one injection will be included in the SAF to account for safety in all participants receiving any injection.

For analyses and displays based on SAF, participants will be classified according to the actual treatment received. Erroneously-treated participants (e.g., those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who has once or on several occasions received active IMP is classified as active.

5.5. PHARMACOKINETIC ANALYSIS SET

The PK analysis set will contain all participants in the PAS who received at least one injection of AZD7442 components and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post dose. Per the protocol a dose is two injections, but any participant receiving one injection will be accounted for in the corresponding individual mAb component.

For analyses and displays based on PK analysis set, participants will be included according to the actual treatment received. Participants who received placebo will not be included. Participants should be excluded from the PK analysis set if they were randomized to AZD7442 and instead received placebo, were randomized to placebo and instead received AZD7442, or received two injections of the same mAb component. Summaries will be displayed by the individual mAb components, AZD8895 and AZD1061. Participants who received only one mAb component should be excluded from both the AZD7442 total summary and the summary of the mAb component they did not receive.

5.6. ADA EVALUABLE ANALYSIS SET

The ADA evaluable analysis set will contain all participants in the SAF who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result. This analysis set is not defined in the protocol but is required for the analyses.

5.7. NAB EVALUABLE ANALYSIS SET

The SARS-CoV-2 nAb evaluable analysis set will contain all participants in the SAF from whom blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum titer observation post dose. Participants should be excluded from the SARS-CoV-2 nAb evaluable analysis set if they were randomized to AZD7442 and instead received placebo, were randomized to placebo and instead received AZD7442, received two injections of the same mAb component, or received only one mAb component. This analysis set is not defined in the protocol but is required for the analyses.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of the dose of IMP i.e., Day 1.

Study Day will be computed as follows:

- Study Day = (Date of event – Date of dose of IMP) + 1 if the date of the event is on or after the date of the dose of IMP;
- Study Day = (Date of event – Date of dose of IMP) if the date of the event is prior to the date of dose of IMP.

In the situation where the event date is partial or missing, Study Day and any corresponding durations will be displayed as missing in the listings.

For illness visits, an illness study day will be calculated. The reference start date is defined as the day of first illness assessment, i.e., illness visit Day 1. This will be calculated separately for each illness episode.

Illness Study Day will be computed as follows:

- Illness Study Day = (Date of event – Date of illness visit Day 1) + 1.

Partial dates

Partial dates for unblinding and COVID-19 vaccination/COVID-19 preventative product in which the month and/or year are missing are not expected. However, imputation rules are specified as follows: in cases where the day is missing, then day will be imputed as the first of the month. In cases where the month is missing, then month will be imputed as the later of January or month of IMP administration. If the date is completely missing, the date will be imputed as the day after IMP administration.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the dose of IMP. In the case where the last non-missing measurement and the date and time of the dose of IMP coincide or where time is missing, that measurement will be considered baseline, but adverse events (AEs) and medications commencing on the date and time of the dose of IMP will be considered post-baseline.

Illness Visit baseline is defined as the first non-missing measurement taken on Illness Visit Day 1. If there is no non-missing measurement available on Illness Visit Day 1, Illness Visit baseline is considered as missing. For instances where Illness Visit Day 1 occurs on the same day as a main study Visit, and Illness Visit Day 1 measurements are missing, then the measurements from the main study Visit will be used as Illness Visit baseline. Otherwise if there is still no available measurement for Illness Visit Day 1, Illness Visit baseline is considered as missing.

6.3. UNSCHEDULED VISITS, RETESTS, AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled, retest (same visit number assigned), and early termination measurements will not be included in by-visit summaries but might contribute to the baseline timepoint and/or maximum value, where required (e.g. shift table). Visits for human biological samples data will follow a windowing convention as described in Section 6.4.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis value for a given study visit for human biological samples data analyses. The window definitions as following will be used for the following assessments:

- Main study: serum sample for SARS-CoV-2 serology (anti-nucleocapsid testing)
- Main study: serum sample for AZD7442 pharmacokinetic assessment (PK)
- Main study: serum sample for AZD7442 ADA assessment (ADA)
- Main study: serum sample for SARS-CoV-2 nAbs assessment (pharmacodynamic [PD])
- Main study: serum sample exploratory biomarkers
- Main study: participant subset only: nasal adsorption for exploratory assessments (PK)
- Illness visits schedule: saliva sample for viral shedding
- Illness visits schedule: serum sample for AZD7442 pharmacokinetic assessment (PK)
- Illness visits schedule: serum sample for SARS-CoV-2 nAbs assessment (PD)
- Illness visits schedule: nasal adsorption for SARS-CoV-2 mucosal responses and exploratory assessments (PK)
- Illness visits schedule: serum sample for exploratory assessments

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

Table E: Analysis windows for serum sample for SARS-CoV-2 serology testing and serum sample exploratory biomarkers by Visit

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1

Day 8	8	2 - 18
Day 29	29	19 - 43
Day 58	58	44 - 74
Day 92	92	75 - 137
Day 183	183	138 - 274
Day 366	366	≥ 275

Table F: Analysis windows for serum sample for AZD7442 PK assessment and serum sample for SARS-CoV-2 nAbs assessment (PD)

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 8	8	2 - 18
Day 29	29	19 - 43
Day 58	58	44 - 74
Day 92	92	75 - 137
Day 183	183	138 - 274
Day 366	366	275 - 411
Day 457	457	≥ 412

Table G: Analysis windows for serum sample for AZD7442 ADA assessment by Visit

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 29	29	2 - 43
Day 58	58	44 - 120
Day 183	183	120 - 274
Day 366	366	275 - 411
Day 457	457	≥ 412

Table H: Analysis windows for nasal adsorption for exploratory assessments by Visit

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 8	8	2 - 49
Day 92	92	50 - 137
Day 183	183	138 - 274
Day 366	366	≥ 275

Table I: Analysis windows for serum sample for AZD7442 PK, serum sample for SARS-CoV-2 nAbs assessment (PD), and serum sample for exploratory assessments by Visit (Illness Visit Schedule)

Visit	Day Relative to Illness	Visit Window (Illness Day)
Illness Day 1	≤ 1	≤ 1

Illness Day 14	14	8 - 17
Illness Day 21	21	18 - 24
Illness Day 28	28	25 - 35

Table J: Analysis windows for Viral Shedding by Visit (Illness Visit Schedule)

Visit	Day Relative to Illness	Visit Window (Illness Day)
Illness Day 1	≤ 1	≤ 1
Illness Day 3	3	2 - 3
Illness Day 5	5	4 - 6
Illness Day 8	8	7 - 9
Illness Day 11	11	10 - 12
Illness Day 14	14	13 - 17
Illness Day 21	21	18 - 24
Illness Day 28	28	25 - 35

Table K: Analysis windows for nasal adsorption for exploratory assessments by Visit (Illness Visit Schedule)

Visit	Day Relative to Illness	Visit Window (Illness Day)
Illness Day 1	≤ 1	≤ 1
Illness Day 14	14	8 - 20
Illness Day 28	28	21 - 35

For assessments occurring during the Illness Visit Schedule, windows are applied only to illness episodes with laboratory confirmed positive RT-PCR test results. One or more results for a particular human biological samples variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

- Change from baseline = Test value at post-baseline visit – Baseline value

Percent change from baseline will be calculated as:

- Percent change from baseline (%) = (Change from baseline at post-baseline visit / Baseline value) * 100%

Change from baseline for Illness Visits will be calculated as:

- Change from baseline at Illness Visit Day 1 = Test value at Illness Visit Day 1 – Baseline value
- Change from baseline at Illness Visits after Illness Visit Day 1 = Test value at post Illness Visit – Illness Visit baseline value

Percent change from baseline at Illness Visits will be calculated as:

- Percent change from baseline Illness Visit Day 1 (%) = (Change from baseline at Illness Visit Day 1/ Baseline value) * 100%
- Percent change from baseline at Illness Visits after Illness Visit Day 1 (%) = (Change from baseline at post-baseline Illness Visit / Illness Visit baseline value) * 100%

If baseline is not available, the change from baseline and percent change from baseline will not be calculated and will remain missing.

7. STATISTICAL CONSIDERATIONS

For continuous data, descriptive statistics (i.e., n [number of participants with available data], mean, standard deviation [SD], median, minimum, maximum, and quartile values) will be presented by treatment group and visit, when applicable. For concentration data and log-transformed data, descriptive statistics (i.e., n [number of participants with available data], n < lower limit of quantification (LLOQ) [number of participants with results below the limit of quantification], geometric mean, arithmetic mean, SD, co-efficient of variation, median, min and max) will be presented by treatment group and visit, when applicable.

For categorical data, the number and percentages of participants in each category will be presented by treatment group and visit, when applicable. The denominator for percentage calculation is the underlying analysis set population unless otherwise stated.

7.1. SAMPLE SIZE CALCULATION

Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single IM dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) (the active group, n = approximately 3433) or saline placebo (the control group, n = approximately 1717) on Day 1.

The sample size calculations are based on the primary efficacy endpoint and were derived following a modified Poisson regression approach (Zou 2004). All participants will be followed for the entire duration of the study.

With at least 18 observed events, assuming 80% true efficacy, the study will have approximately 90% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than 0 (see Table L:).

Table L: Simulated Power by Number of Observed Events

$\lambda_{Placebo}$	$\lambda_{AZD7442}$	Observed Events	Simulated Power
0.0074	0.0015	18	89%
0.0082	0.0016	20	96%
0.0090	0.0018	22	97%
0.0098	0.0020	24	98%

Simulated power is based upon 10000 simulations of trials assuming 80% efficacy $\left(1 - {\lambda_{AZD7442}}/{\lambda_{Placebo}}\right)$, using Poisson regression model with robust variance, with no participants lost follow-up. Power is the proportion of trials with p-value < 0.05.

The sample size necessary to achieve the power for the primary endpoint is calculated based on the assumed attack rate in the placebo group and the 80% efficacy assumption, using Poisson regression model with robust variance.

7.2. MISSING DATA

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.4, and 16.3.2 of this analysis plan.

Partially or completely missing medication dates will be handled as described in APPENDIX 1.

7.3. STATISTICAL TESTS

Statistical tests will be conducted at the two-sided 5% significance level. Confidence Intervals (CIs) will be two-sided with 95% coverage.

The null hypothesis for the primary endpoint is: efficacy of AZD7442 compared to placebo in preventing COVID-19 is equal to 0. Whereas, the alternative hypothesis is: efficacy of AZD7442 compared to placebo in preventing COVID-19 is not equal to 0. That is:

H0: efficacy = 0

HA: efficacy ≠ 0

Primary efficacy will be presented with a 2-sided 95% CI, and statistical significance will be achieved if the lower bound of the 2-sided 95% CI is > 0. The success criterion for the study will be statistical significance.

If the statistical significance of the primary efficacy endpoint is demonstrated at two-sided alpha of 0.05, formal assessments of the key supportive estimands and key secondary estimand will be conducted at the primary analysis.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

A hierarchical approach will be used to control for multiplicity of the primary, key supportive, and key secondary analyses. That is, the null hypotheses for these efficacy analyses will be tested in a hierarchical order, and the

subsequent null hypothesis will be tested at a significance level of 0.05 (two-sided) only if the prior null hypothesis is rejected (i.e., the treatment effect on the efficacy endpoint is demonstrated at the significance level of two-sided 0.05). The hierarchical approach will include the below analyses as ordered:

1. The primary efficacy endpoint will be assessed at the primary analysis, using the primary estimand, after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs earlier. All primary endpoint events accrued up until data cut-off will be included in the primary analysis.

2. If the statistical significance of the primary efficacy endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the first key supportive estimand (treatment policy strategy) will be conducted also at the primary analysis.

3. If the statistical significance of the first key supportive analysis of the primary endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the second key supportive estimand (including death due to any cause) will be conducted also at the primary analysis.

4. If the statistical significance of the second key supportive analysis of the primary endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the key secondary efficacy endpoint will be conducted also at the primary analysis.

Only nominal p-values will be provided for the other secondary and exploratory efficacy endpoints. No statistical testing will be performed for the safety endpoints.

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Data from all centers will be pooled together in the analyses and there are no plans to perform an analysis of homogeneity of the results across centers.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The analyses will be adjusted for the following covariates and factors. For details of their inclusion in the models, refer the Sections 16.1.3 and 16.2.5.

- Categorical age (years) at randomization from the Electronic Data Capture (EDC) system (≥ 60 and < 60).

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Section 16.1.7. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The list of subgroups includes but may not be limited to:

- Categorical age (years) at informed consent (3 groupings 1: ≥60 years and <60 years, 2: ≥65 years and <65 years, 3: ≥75 years and <75 years);
- Residence in long-term care facility (yes and no);
- Increased risk of exposure to infection with SARS-CoV-2 (yes and no);
- Increased risk for inadequate response to active immunization (yes and no);
- Sex (male and female);
- Region (North America, United Kingdom, and European Union);
- Country (United States, United Kingdom, Belgium, France, Spain);
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- COVID-19 co-morbidities at baseline (at least one co-morbidity, no co-morbidity);
- High Risk for severe COVID-19 at baseline (History of Obesity, Obese (baseline BMI≥30), Morbid Obesity (baseline BMI≥40), Chronic kidney disease (CKD), Diabetes, Immunosuppressive disease, Immunosuppressive treatment, Cardiovascular disease (CV disease), Chronic obstructive pulmonary disease (COPD), Chronic liver disease, Hypertension, Asthma, Cancer, Smoking, Sickle cell disease) (yes/no; refer to APPENDIX 1 for description of each condition).

If models of subgroup analysis do not converge due to sparse data, changes to planned subgroup analysis will be described in the CSR.

Subgroup data will be obtained from the EDC system for items collected in both EDC and Interactive Response Technology (IRT).

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. OUTPUT PRESENTATIONS

APPENDIX 2 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore, the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Number of participants screened will be presented overall for the PAS. Number and percentage of participants with screen failure and reason for screen failure will also be presented overall based on the PAS. Number of participants randomized will be presented overall and by treatment group for the PAS.

Number and percentages of participants dosed, discontinued early from IMP (including reason for not receiving both injections), ongoing in study (for primary analysis only), who discontinued early from the study (including reason for withdrawal), and who became unblinded to received treatment (including reason for unblinding) will be provided overall and by planned treatment group based on the FAS.

The number of participants included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by planned treatment group based on the FAS. A listing showing inclusion and exclusion of each participant from each analysis set, including reason for exclusion, will be provided.

9.2. PROTOCOL DEVIATIONS

Number and percentage of participants with important protocol deviations, as identified by the study team in a blinded fashion before the DBL, will be provided overall and by planned treatment group based on the FAS for each category of protocol deviations specified in the Protocol Deviations Management Plan.

A listing of protocol deviations identified by the study team (important or not) will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – collected at informed consent
- Age groups (≥18 to <60 years, ≥60 to <70 years, ≥70 to <80 years, and ≥80 years; ≥60 years, ≥65 years, and ≥75 years)
- Sex (refer to Section 7.7)
- Race (refer to Section 7.7)
- Ethnicity (refer to Section 7.7)
- Weight (kg)

- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- BMI group (kg/m^2) (<18.5, ≥18.5 - <25, ≥25 - <30, ≥30 - <40, and ≥40)
- Screening result from NP swab for SARS-CoV-2 RT-PCR (positive, negative)
- Smoking status (current, former, never)
- ECOG performance status (0, 1, and >1)
- Home or other confinement status (yes/no)
- Country (refer to Section 7.7)
- High Risk for severe COVID-19 at baseline (History of Obesity, Obese (baseline BMI≥30), Morbid Obesity (baseline BMI≥40), CKD, Diabetes, Immunosuppressive disease, Immunosuppressive treatment, CV Disease, COPD, chronic liver disease, Hypertension, Asthma, Cancer, Smoking, Sickle cell disease) (yes/no)
- COVID-19 risk assessment data as collected on the eCRF
- Subgroups specified in Section 7.7 and not previously listed above

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics overall and by planned treatment group based on the FAS and FPAS. For categorical demographic and other baseline characteristics, number and percentage of participants in each category will be provided overall and by planned treatment group based on the FAS and FPAS. If there are major differences between the FAS and the SAF, the summaries will be repeated and presented by actual treatment group for the SAF. No statistical testing will be carried out for demographic or other baseline characteristics.

All demographic and risk assessment data will be listed.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as follows:

- BMI (kg/ m^2) = weight (kg)/ [height (m)^2]

11. MEDICAL HISTORY

Medical history is defined as any medical conditions/diseases that started and stopped before the first dose of IMP.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1 or higher, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) overall and by planned treatment group based on the FAS. A participant having more than one medical condition/disease within the same

SOC/PT will be counted only once for that SOC or PT.

COVID co-morbidities are collected on the Medical history page of the eCRF. The number and percentage of participants with each co-morbidity and also with any co-morbidities will be summarized overall and by planned treatment group based on the FAS.

All medical history will be listed.

12. CONCOMITANT ILLNESSES

Concomitant conditions/illnesses are defined as any medical conditions/illnesses that started before the first dose of IMP AND were ongoing at the time of the dose of IMP or ended on date of dose.

Concomitant conditions/illnesses will be coded using the MedDRA, version 23.1 or higher, and will be summarized by SOC and PT overall and by planned treatment group based on the FAS. A participant having more than one medical condition/illness within the same SOC or PT will be counted only once for that SOC or PT.

All concomitant conditions/illnesses will be listed.

13. MEDICATIONS

Prior medications are defined as any medication that started and stopped prior to the dose of IMP.

Concomitant medications are defined as:

- Any medication that started before the dose of IMP AND was ongoing at the time of the dose of IMP or ended on the date of dose of IMP;
- Any medication that started on or after the dose of IMP.

Partially or completely missing medication start and stop dates will be handled as described in APPENDIX 1.

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020, or a more recent version.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by planned treatment group based on the FAS. A participant having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

All collected prior and concomitant medications will be listed.

14. EXPOSURE TO STUDY INTERVENTION

Due to the simplicity of dosing for this study, exposure is summarized in the participant disposition table. All exposure data will be listed.

15. COMPLIANCE WITH STUDY INTERVENTION

Compliance will not be calculated since participants receive a single dose (2 IM injections) within clinic.

16. EFFICACY ENDPOINTS

Unless otherwise indicated, all efficacy summaries and figures will be presented based on the FPAS.

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. The primary efficacy endpoint is to be to be assessed after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs earlier.

Participants will be included as an event in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 prior to Day 183 and present with at least one of the qualifying symptoms in Table M:. The onset of symptoms will commonly occur between 2 and 8 days of infection with detectable virus typically up to 15 days. To maintain the relationship between the RT-PCR sample and symptoms the sample should be collected on or close to the symptom assessment but must be collected within 5 days prior or 10 days following the assessment of qualifying symptoms. This duration will allow participants time to assess and confirm symptoms under medical supervision after the onset of symptoms, which will typically, but not always, occur at Illness Visit Day 1. A positive SARS-CoV-2 RT-PCR will be defined based on the central laboratory result whenever both central and local laboratory results are available for nasopharyngeal (NP) swabs, or if only a central lab NP swab result is available. If only a local NP swab laboratory result is available, then the local laboratory result will be used. If neither central nor local NP swab laboratory results are available, a saliva sample taken within window during Illness Visits will be used to determine the RT-PCR result. If no SARS-CoV-2 RT-PCR results are available, the participant will be considered as not having met the primary endpoint. Data from the eCRF will be used to determine if the participant met the qualifying symptoms. If a participant's first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurs on or after Day 183, the participant will be considered as not having met the primary endpoint.

Table M: COVID-19 Qualifying Symptoms

Duration	Symptom
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
	New onset confusion (only for participants ≥ 60 years old)
	Appetite loss or decrease food intake (only for participants ≥ 60 years old)
	Increased supplemental oxygen requirement (only for participants ≥ 60 years old on baseline supplemental oxygen)
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea

Adapted from (CDC, 2020)
CDC, Centers for Disease Control and Prevention

16.1.2. MISSING DATA IMPUTATION METHOD FOR PRIMARY EFFICACY ENDPOINT

No missing data imputation method will be used for primary efficacy analysis. For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint. Participants will be censored (considered as not having the event) at the time of last observation.

Sensitivity analyses will be explored to assess the robustness of treatment effects for the primary efficacy endpoint, where different missing data mechanisms will be explored using multiple imputation approaches. Full details of the sensitivity analyses are specified in Section 16.1.5.

16.1.3. PRIMARY ESTIMAND

The treatment condition of interest is single dose of AZD7442 (two IM injections, one for each mAb component, AZD8895 and AZD1061). The alternative treatment condition to which comparison will be made is a placebo.

The population of participants targeted in the primary estimand includes adults at least 18 years of age who have not had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection and who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.

The primary endpoint (variable) to be obtained is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183.

The primary estimand uses a while on treatment strategy. Data for participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, are censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier.

The population-level summary measure is prophylactic efficacy, calculated as 1 − relative risk (RR). (RR is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.1.4. PRIMARY ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The primary efficacy analysis of the primary endpoint will be performed on the FPAS. Participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint will be censored (considered as not having the event) at the time of last observation. Participants with deaths that are caused by SARS-CoV-2 (death related to COVID marked on the death eCRF page) will be considered as having the event, even if no other qualifying symptoms are met. Participants with hospitalizations due to COVID-19 will also be considered as having the event.

A Poisson regression model with robust variance (Zou, 2004) adjusting for follow-up time, will be used as the primary efficacy analysis model to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP between the AZD7442 and the placebo groups. The model contains the planned treatment group and age group at the time of informed consent (i.e., ≥ 60 years and < 60 years, see Section 7.6) as a covariate. The logarithm of the participant's corresponding follow-up time at risk starting from dose up to the study day 183 visit will be used as an offset variable in the model to adjust for participants having different exposure times during which the events occur. Participants who withdraw or have a non-COVID-19 related death prior to meeting the primary endpoint will not be counted as having the event. The follow up time for those participants will be at that time relative to dose. Calculation of follow-up time is detailed as following:

- For participants who meet the primary endpoint before Day 183, the follow-up time will be calculated as (Date of Onset of Primary Endpoint) – (Date of Dosing) + 1. Date of Onset of Primary Endpoint is defined as the assessment date of qualifying COVID symptoms, if associated with a positive SARS-CoV-2 RT-PCR lab test from a sample collected within the 5 days prior to symptom assessment through 10 days after symptom assessment. In the case of death due to COVID-19 or hospitalization due to COVID-19, the Date of Onset of Primary Endpoint is the earliest date of death/date of hospital admission when a qualifying symptom assessment is not observed.
- For participants who do not experience a primary endpoint before Day 183, the efficacy follow-up time will be considered censored and determined based on the following:
    - If an end of study date occurs prior to Day 183, the efficacy follow-up time will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) + 1.
    - If an end of study date occurs after Day 183, the efficacy follow-up will be censored at Day 183.

For participants who continue to participate in the study at the time of the primary analysis, the DCO date will be used as their last assessment date. For participants with no post-baseline visit data available, the date of IMP administration will be used i.e. follow-up will be 1 day.

Efficacy is the incidence of infection in the AZD7442 group relative to the incidence of infection in the placebo group, expressed as a percentage. Efficacy will be calculated as relative risk reduction (RRR) = 100% x (1 - relative risk).

RRR and its corresponding 2-sided 95% CI will be estimated from the Poisson regression model with robust variance. In addition, the 2-sided p-value testing null hypothesis that there is no difference in efficacy between AZD7442 and placebo (i.e. the efficacy is equal to 0) will be obtained from the model. Statistical significance will be achieved if the lower bound of the 95% CI for efficacy is > 0, which corresponds to an observed two-sided p-value < 0.05. For the final analysis nominal 95% CI's will be presented.

The Poisson regression with robust variance analysis will be implemented by using the SAS PROC GENMOD procedure with the REPEATED statement for participant ID and logarithm link as well as OFFSET option. The estimated parameter $\hat{\beta}$[i.e., log(RR)], 2-sided 95% confidence interval (CI) for $\hat{\beta}$, and the 2-sided p-value will be obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RRR is given by [(1 – exp($\hat{\beta}$)) * 100%]. The CI for the percent of RRR is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If convergence cannot be achieved with the Poisson regression analysis model with robust variance, the Cochran-Mantel-Haenszel (CMH) will be used as the primary analysis model to test the treatment effect on SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD7442 and placebo groups. The CMH test will be stratified by age group at the time of informed consent (i.e., ≥ 60 years and < 60 years, see Section 7.6). The RR of AZD7442 over placebo for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose and the 95% CI will be obtained. The percent of RRR and the 95% CI will be reported following the relationship of RRR

(%) = (1- RR) * 100%. A Breslow-Day test will be conducted, and p-value presented, to evaluate homogeneity of the RRR across strata.

A listing will be provided for all COVID-19 symptom assessments and NP swabs assessed by RT-PCR (both local laboratory and central laboratory samples) regardless of RT-PCR result.

16.1.5. SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

As a sensitivity analysis to the handling of missing data in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint (Section 16.1.4) will be repeated with multiple imputation for intercurrent events. For participants who are in FPAS but (1) do not have a SARS-CoV-2 RT-PCR-positive symptomatic illness status occurring post dose of IMP and withdraw from the study prior to the time of analysis, or (2) were unblinded to treatment assignment prior to having met the criteria for the primary efficacy endpoint, or (3) received COVID-19 vaccine or other preventive product prior to having met the criteria for the primary efficacy endpoint, their event status will be imputed assuming the observed event rate per treatment group conditional on stratification factors using multiple imputation techniques as described in the following paragraphs.

The primary analysis using Poisson regression with robust variance requires a participant-level dataset. A repeated imputation approach is introduced to impute the status of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP for missing observations at the participant level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). In the primary analysis the missing outcome for participants who drop out (e.g., withdrawal, lost to follow-up, death not caused by SARS-CoV-2, etc.) prior to reaching cut-off time for analysis without a SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP will be imputed per stratum determined by the stratification factor using observed event rate per treatment group. The imputation and subsequent analysis may be carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described as follows.

- Step 1: Missing events in both arms will be imputed with the observed event rate per treatment group. The imputation may be executed using SAS PROC MI (logistic regression method with the recoded treatment term and stratification factor), or random sampling from an appropriate distribution. The random seed is 10021.
- Step 2: A complete dataset comprises the imputed SARS-CoV-2 RT-PCR-positive symptomatic illness status and observed SARS-CoV-2 RT-PCR-positive symptomatic illness status.
- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD7442 and placebo, with the term of treatment group and the stratification factor. The point estimate of log-transformed RR and its variance will be extracted from the model.
- Steps 1-3 will be repeated 20 times. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, that will result in a combined point estimate of log-transformed RR and the

variance.

A sensitivity analysis of the primary endpoint, in which participants who were seropositive by any test for SARS-CoV-2 pre-dose of IMP are excluded, may be performed.

16.1.6. SUPPLEMENTARY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

As a supplementary analysis, the primary analysis of the primary efficacy endpoint (refer to Section 16.1.4) will be repeated including region (Section 7.7) as an additional covariate to assess the robustness of the efficacy results, if data permit.

To support the primary analysis, time to event (i.e., the duration in days from dose to first event or censoring) analyses will be performed as follows. A Cox proportional hazard (PH) model, stratified by age group at informed consent (Section 7.6) with treatment group as the only covariate, will be fitted to the data, and the Efron method will be used to control for ties. The hazard ratio and corresponding 95% CI from the Cox PH model will be presented. Kaplan-Meier curves with log-rank test p-value will also be presented by treatment arm.. Corresponding descriptive statistics for the active and control groups will also be produced.

In addition, the absolute risk reduction of AZD7442 over placebo in preventing the incidence of the SARS-CoV-2 RT-PCR positive symptomatic illness prior to Day 183 will be presented, along with the 2-sided 95% CI using the Miettinen and Nurminen's score method (Miettinen and Nurminen, 1985). The absolute risk reduction (ARR) will be implemented using the SAS PROC FREQ procedure.

16.1.7. SUBGROUP ANALYSES FOR PRIMARY EFFICACY ENDPOINT

Subgroup analysis will be performed for the primary efficacy endpoint, SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. For subgroup analysis, FPAS will be used. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model adjusting for follow-up time with the terms of planned treatment, age group (Section 7.6), subgroup, and treatment-by-subgroup interaction, which will be implemented using PROC GENMOD procedure. If this full model does not achieve convergence, a reduced model of planned treatment, subgroup, and treatment-by-subgroup interaction will be considered. Within each level of a subgroup, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RRR and the 95% CI will be presented. If the CMH model is used for primary analysis (e.g. if the Poisson regression model fails to converge), a CMH model will also be used for subgroup analyses to generate the RRR and the corresponding 95% CI.

The subgroup analysis will be conducted for the subgroups in Section 7.7 on the FPAS population.

For subgroups corresponding to one of the factor levels included in the analysis model, the corresponding factor will not be included in the model. For example, the age group factor will not be included in the model for the analysis of participants < 60 years old at the time of informed consent subgroup and analysis of participants ≥ 60 years old at

the time of informed consent subgroup.

No adjustment to the significance level for testing of all these subgroup analyses will be made since all these analyses will be considered supportive of the primary analysis.

16.1.8. ADDITIONAL ESTIMANDS FOR PRIMARY EFFICACY ENDPOINT

Additional estimands will also be used for the primary efficacy as shown in Table N:.

Table N: List of Additional Estimands for Primary Efficacy

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183 – Hypothetical Estimand	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.	For participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, only data prior to the intercurrent event (i.e., up to the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier) will be considered and data after the intercurrent event will be imputed (i.e., intercurrent events will be handled using hypothetical strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
				See Section 16.1.8.1.	
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183 – Principal Stratum Estimand	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be excluded from analysis (i.e., intercurrent events will be handled using principal stratum strategy). The principal stratum is the stratum of participants who did not experience an intercurrent event independent of randomized treatment assignment.	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
The efficacy	A subset of the full pre-exposure analysis set,	Single dose of	A binary	Participants who become	Prophylactic

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183 – Per Protocol Estimand	defined as all participants who were randomized, received a full dose of IMP, who did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, and who have no significant deviations from the protocol prior to Day 183 or meeting the primary endpoint (whichever occurs first). Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.	AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.	unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).	efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.1.8.1. Hypothetical Estimand

The treatment condition of interest is single dose of AZD7442 (two IM injections, one for each mAb component, AZD8895 and AZD1061). The alternative treatment condition to which comparison will be made is a placebo.

The population of participants targeted in the primary estimand includes adults at least 18 years of age who have not had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection and who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.

The primary endpoint (variable) to be obtained is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183.

The population-level summary measure is prophylactic efficacy, calculated as 1 − relative risk (RR). (RR is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

For participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for endpoint, only data prior to the intercurrent event (i.e., up to the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier) will be considered and data after the intercurrent event will be imputed (i.e., intercurrent events will be handled using hypothetical strategy). A single imputation from the Bernoulli distribution will be used, where the probability that the participant experiences the primary endpoint is the event rate observed in the subset of participants who did not have an intercurrent event in the same arm. The detailed imputation steps are described as follows.

- If the participant experiences a primary endpoint event then no imputation is required, and data is considered up to the Date of Onset of Primary Endpoint (Section 16.1.4).
- If the participant does not experience a primary endpoint event and also has no intercurrent event, then no imputation is performed, and data is considered up to Date of End of Study or Date of Last Assessment, whichever is later. If an end of study date or date of last assessment occurs after Day 183, the efficacy follow-up will be censored at Day 183. For participants who continue to participate in the study at the time of the primary analysis, the DCO date will be used as their last assessment date. For participants with no post-baseline visit data available, the date of IMP administration will be used i.e. follow-up will be 1 day.
- If the participant has an intercurrent event before Day 183 and before a primary endpoint event:
    - Step 1: The missing event status will then be imputed using a single imputation from the Bernoulli distribution, where the probability that the participant experiences the primary endpoint is the event rate observed in the subset of participants who did not have an intercurrent event in the same arm and age group. For participants in the placebo group: $p_{Placebo} = \frac{E_{Placebo,no\ IE}}{N_{Placebo,no\ IE}}$, where: $E_{Placebo,no\ IE}$ is the

number of participants in the placebo arm who experience a primary endpoint event and did not experience an intercurrent event; $N_{Placebo,no\ IE}$ is the number of participants in the placebo arm who did not experience an intercurrent event. The value of $p_{Placebo}$ will be calculated separately for each age group within the placebo arm. For participants in the AZD7442 group: $p_{AZD7442} = \frac{E_{AZD7442,no\ IE}}{N_{AZD7442,no\ IE}}$, where: $E_{AZD7442,no\ IE}$ is the number of participants in the AZD7442 arm who experience a primary endpoint event and did not experience an intercurrent event; $N_{AZD7442,no\ IE}$ is the number of participants in the AZD7442 arm who did not experience an intercurrent event. The value of $p_{AZD7442}$ will be calculated separately for each age group within the AZD7442 arm. If there are zero events observed in a given age group in a given arm, then the event rate used for imputation will be the arm-specific event rate (pooled across both age groups). The random seed is 23456.

- Step 2: The follow-up time will be calculated as described in Section 16.1.4. For participants who previously had an intercurrent event prior to meeting the primary endpoint and now have an imputed primary endpoint event, the Date of Onset of Primary Endpoint will be the date of the first intercurrent event.
- Step 3: Analyze the complete hypothetical estimand dataset using a Poisson regression model with robust variance as described in Section 16.1.4. Participants with an observed event or an imputed event are both included as events, and participants without an observed event or without an imputed event are no included as primary endpoint events.
- Step 4: Repeat steps 1 through 3 above 100 times. The reported effect size will be the average of the results from the 100 analyses using the imputed datasets.

16.1.9. KEY SUPPORTIVE ANALYSES OF PRIMARY EFFICACY ENDPOINT

As key supportive analyses, the primary analysis of the efficacy endpoint (refer to Section 16.1.4) will be repeated using two key supportive estimands: one, which utilizes a treatment policy strategy for intercurrent events , and a second, which includes death due to any cause in the primary endpoint. These analyses are included in the multiple testing hierarchy described in Section 7.4. The attributes of the key supportive estimands are described in Table O: and Table P:.

Table O: List of First Key Supportive Estimand Attributes

Label	The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183 – Treatment Policy Estimand
Definition Population	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR

	having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
Treatment Condition of Interest	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo
Variable/Endpoint	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.
Intercurrent event handling strategy	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be included and analyzed regardless (i.e., intercurrent events will be handled using a treatment policy strategy).
Population-level summary measure	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

Table P: List of Second Key Supportive Estimand Attributes

Label	The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183 – All-Cause Mortality Estimand
Definition Population	Full pre-exposure analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, and did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. Targeted participants will have the following characteristics: Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
Treatment Condition of Interest	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo
Variable/Endpoint	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause occurs

	post dose of IMP and prior to Day 183.
Intercurrent event handling strategy	Participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).
Population-level summary measure	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.2. SECONDARY EFFICACY

The key secondary efficacy endpoint is:

- The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies

The other secondary efficacy endpoints are:

- The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post dose of IMP
- The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP

Please refer to Section 17 for other secondary endpoints related to PK and ADA data.

16.2.1. KEY SECONDARY EFFICACY ENDPOINT

The key secondary endpoint is the incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

The primary and the key secondary efficacy hypotheses will be assessed by a hierarchical order. More details on multiplicity are provided in Section 7.4.

16.2.2. ESTIMANDS FOR KEY SECONDARY EFFICACY

The treatment condition of interest is single dose of AZD7442 (two IM injections, one for each mAb component, AZD8895 and AZD1061). The alternative treatment condition to which comparison will be made is a placebo.

The population of participants targeted in the key secondary estimand includes adults at 18 years of age who have not had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection and who are candidates for benefit

from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.

The key secondary endpoint (variable) to be obtained is a binary response, whereby a participant is defined as post-baseline positive if the participant has a positive serology test result for SARS-CoV-2 nucleocapsid antibodies from the validated assay performed at the central laboratory.

The estimand for the key secondary efficacy endpoint uses a while on treatment strategy. Data for participants who become unblinded to treatment assignment and/or take COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the key secondary efficacy endpoint, are censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier.

The population-level summary measure is prophylactic efficacy, calculated as 1 − relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.2.3. OTHER SECONDARY EFFICACY ENDPOINTS

The following endpoints will be presented along with 95% CIs and p-values. These will be nominal, as they are not controlled for multiplicity.

16.2.3.1. The Incidence of SARS-CoV-2 RT-PCR-Positive Severe or Critical Symptomatic Illness Occurring Post Dose

The severity of COVID-19 will be evaluated in participants who test positive for SARS-CoV-2 by RT-PCR. A diagnosis of severe or critical COVID-19 will include laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus meeting the severity criteria. The calculation of the follow up time (included as offset in model) will be calculated by using date symptoms become severe as the reference date.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, OR dyspnea, AND lung infiltrates) or hypoxemia (SpO2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher. Data from the eCRF will be used to determine if the participant met the qualifying severe symptoms.

All COVID-19 severity data will be listed.

16.2.3.2. The Incidence of COVID-19-Related Emergency Department Visits Occurring After Dosing with IMP

Incidence of COVID-19-related Emergency Department visits is collected on the Emergency Room visit eCRF form. If there is any record with hospitalization status as ER with primary reason for ER visit selected as ‘COVID-19 related symptoms’, it is considered that the participant has an incidence of COVID-19-related emergency

department visit. The calculation of the follow-up time (included as offset in model) will be calculated by using the earliest start date of ER visit.

All Emergency Department visit data will be listed, regardless of primary reason for ER visit.

16.2.4. Missing Data Imputation Method for Secondary Efficacy Endpoints

No imputation method will be used for the main analysis of the key secondary efficacy endpoint or for any analysis of other secondary efficacy endpoints.

16.2.5. Analysis of Secondary Efficacy Endpoints

The key secondary efficacy endpoint will be analyzed as described in Section 16.2.1.

All other secondary efficacy endpoints described in Section 16.2.3 above will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.4), prior to Day 183. These analyses will be repeated for these endpoints through Day 183 and through Day 366.

The key secondary efficacy endpoint will be assessed by a hierarchical order. More details on multiplicity control are described in Section 7.4. For the other secondary efficacy endpoints, the 95% CIs and p-values will be nominal as they are not controlled for multiplicity.

16.2.6. Sensitivity Analyses for Secondary Efficacy Endpoints

No sensitivity analysis will be performed for any secondary efficacy endpoints.

16.2.7. Supplementary Analyses for Secondary Efficacy Endpoints

For all secondary efficacy endpoints (Section 16.2.3), the incidence of each endpoint will be presented graphically using Kaplan-Meier curves with log-rank test p-value.

16.2.8. SUBGROUP ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

Subgroup analyses for secondary endpoints will be conducted if their sample is sufficient. The same methodology for the primary endpoint will be employed (refer to Section 16.1.7). If the model will not converge because the sample is too small, then only descriptive statistics such as counts and percentages and where applicable continuous summary statistics will be presented.

16.3. Exploratory Efficacy

The exploratory efficacy endpoints are:

- The incidence of the first case of SARS CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366
- Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR (Illness Visits only)
- Duration of SARS-CoV-2 shedding in saliva over time (Illness Visits only)
- Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442 (Illness Visits only)
- Biophysical parameters, including, but not limited to serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28
- Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28.

Only nominal p-values will be provided for exploratory efficacy endpoints (see Section 7.4). Please refer to Section 17 for exploratory endpoints related to PK and PD data.

16.3.1. EXPLORATORY EFFICACY ENDPOINTS

16.3.1.1. The Incidence of the First Case of SARS-CoV-2 RT-PCR-Positive Symptomatic Illness Occurring after Dosing with IMP through Day 366

An exploratory endpoint is the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366. The criteria for determining this endpoint is the same as those for the primary efficacy endpoint (see Section 16.1.1) except that the endpoint will only be evaluated within the specified efficacy evaluation period, through Day 366. The analysis will be performed on the full pre-exposure analysis set. This endpoint will be analyzed as described in Section 16.2.1.

To assess the durability of efficacy analyses for the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366, single-arm descriptive summaries over the Day 366 follow-up period for participants who received AZD7442 with no censoring for unblinding intercurrent events will be presented. However, if a participant receives a COVID-19 vaccine or COVID-19 preventive product, their follow-up will be censored at the date of first administration of that product.

16.3.1.2. Viral Genome Copies in NP Swabs Collected at Illness Visits as Determined by qRT-PCR

An exploratory efficacy endpoint is the viral genome copies in NP swabs which will be collected via SARS-CoV-2 RT-PCR test at central laboratory at Illness Visits as described in protocol section 1.3. The analysis will be performed on the full pre-exposure analysis set. Observed and change from baseline for Illness Visits (as defined in Section 6.5) in viral load will be summarized by planned treatment group and time points for the Illness Visits. A

logistic regression analysis of the proportion of participants with viral load >10^4 copies/mL may be performed. In addition, the number of weeks of high viral load (>10^4 copies/mL) among participants may be performed using a Stratified Wilcoxon rank sum test.

A listing will be provided for all viral genome copy data, regardless of RT-PCR result. Indicators will be included in listings of illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

16.3.1.3. Duration of SARS-CoV-2 Shedding in Saliva Over Time (Illness Visits only)

- Viral Shedding

An exploratory efficacy endpoint is the duration of SARS-CoV-2 shedding in saliva over time. The analysis will be performed on the full pre-exposure analysis set. Saliva samples for viral shedding will be collected at Illness Visits as described in protocol section 1.3. The number and proportion of participants shedding on Illness Visits planned in the protocol Schedule of Assessments will be summarized. Exact 95% CIs using Clopper-Pearson method for binomial proportions will be computed.

The duration of SARS-CoV-2 shedding in saliva will be calculated as following:

Duration (days) = (Date of Illness Visit when viral shedding first tested as persistently negative or date of last Illness Visit when test was positive, if no negative test is available) – Date of first positive + 1.

The number of days of shedding will be summarized by descriptive statistics.

A listing will be provided for all viral shedding data, regardless of RT-PCR result. Indicators will be included in listings of illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

- Viral Quantitation

For values reported as lower than the lower limit of quantification (LLOQ), a value equal to half of the limit of quantification will be imputed in viral quantitation summaries. Missing values will not be imputed in viral quantitation summaries.

For the subset of participants who shed, viral quantities as measured by qRT-PCR will be summarized for Illness Visits planned in the protocol Schedule of Assessments. Summary statistics will be presented describing the mean, standard deviation, median, minimum and maximum of Log10 (viral copies/mL) at Illness Visit baseline (Date of first positive) and each post-baseline time-points.

Change and percent change from Illness Visit baseline at each post-baseline time point will also be summarized.

Time weighted change from Illness Visit baseline to each post-baseline time-point is derived on a by-participant basis using the linear trapezoidal rule with all available data from baseline to that specific time-point minus the baseline value. This is defined as (Area Under the Curve [AUC])/number of days – Illness Visit baseline value, between Illness Visit baseline to that specific post-baseline time-point. AUC from Illness Visit baseline to each post-baseline time-point will be reported as well.

Figures such as Log_{10} (viral copies/mL) over time (mean ± SD), AUC and time weighted change from Illness Visit baseline of Log_{10} (viral copies/mL) over time (box plots) will be provided.

16.3.1.4. Genotypic Analysis and Biochemical and/or Susceptibility Analysis of SARS-CoV-2 Variants to AZD7442 (Illness Visits Only)

An exploratory efficacy endpoint is the Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 from NP swabs collected at Illness Visit baseline. This analysis will not be covered in this SAP.

16.3.1.5. Biophysical Parameters, Including But Not Limited to Serial Measurements of Skin Temperature, Heart Rate, Respiratory Rate, Blood Oxygen Saturation, and Physical Activity, Recorded Using a Biosensor From Illness Visits Day 1 Through Day 28

A group of efficacy endpoints are biophysical parameters collected from Current Health wearable device. The analysis of these exploratory endpoints results is not covered in this SAP.

16.3.1.6. Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28

A group of exploratory endpoints are symptoms collected by participants in an illness e-Diary. Symptoms from the first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose will be summarized. The number and percentage of participants with these symptoms, onset study day of these symptoms, and the duration days will be summarized by treatment group. The analysis will be based on participants in the full pre-exposure analysis set.

All symptoms from each illness visit will be listed, regardless of RT-PCR result. Indicators will be included in listings of illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

16.3.2. MISSING DATA IMPUTATION METHOD FOR EXPLORATORY EFFICACY ENDPOINTS

No imputation method will be used for exploratory efficacy endpoints.

16.3.3. SENSITIVITY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

No sensitivity analysis will be performed for the exploratory efficacy endpoints.

16.3.4. SUPPLEMENTARY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

No supportive analysis will be performed for the exploratory efficacy endpoints.

17. PHARMACOKINETIC, PHARMACODYNAMIC, AND ADA ENDPOINTS

The PK and ADA secondary endpoints are:

- Serum AZD7442 concentrations
- PK parameters, if data permit
- The incidence of ADA to AZD7442 in serum

The exploratory PK and PD endpoints are:

- AZD7442 nasal fluid concentrations
- Post-treatment geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) for neutralizing antibodies (nAbs) to SARS-COV-2 from baseline value through Day 366 after single IM dose in SARS-CoV-2 nAb (wild-type assay or pseudo neutralization assay)

Other exploratory assays for humoral, mucosal and cellular immune responses may be performed based upon emerging safety, efficacy, and PD data.

17.1. ANALYSIS OF PK, PD, AND ADA ENDPOINTS

17.1.1. SERUM AZD7442 CONCENTRATIONS

Individual AZD7442 (AZD8895 and AZD1061) serum concentration data will be listed and tabulated by mAb component, along with descriptive statistics for the PK analysis set. A figure of serum concentrations by mAb component will also be presented.

Pharmacokinetic exposure (i.e., AUCs) and other PK parameters may be estimated using non-compartmental analysis; this will be optional if data permit. Potential correlation between PK exposure and efficacy/safety response may optionally be explored. Population PK analysis may be performed by the Sponsor and reported in a separate report. The analysis is not covered in this SAP.

To demonstrate that there is no difference between the clonal material and the pooled material, a bioequivalence comparison will be conducted. All participants included in the pharmacokinetic analysis set will be used to evaluate comparability between the clonal and pooled material. This analysis is not covered in this SAP.

17.1.2. THE INCIDENCE OF ADA TO AZD7442 IN SERUM

17.1.2.1. ADA Variables

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in protocol section 1.3. ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of nAb will be tested for all ADA-positive samples. The nAb results will be reported as positive or negative. A participant is defined as being ADA-positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise the participant is defined as ADA negative.

The number and percentage of ADA-evaluable participants in the following ADA categories in each treatment group will be determined. The number of ADA-evaluable participants in the treatment group will be used as the denominator for percentage calculation.

- ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence.
- Treatment-induced ADA positive (positive post-baseline and not detected at baseline).
- Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following drug administration).
- Treatment-emergent ADA positive (either treatment-induced ADA positive or treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence.
- ADA positive post-baseline and positive at baseline.
- ADA positive at baseline and not detected post-baseline.
- Treatment-emergent ADA (TE-ADA) persistently positive, defined as treatment-emergent ADA positive participants having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment.
- Treatment-emergent ADA (TE-ADA) transiently positive, defined as treatment-emergent ADA positive participants having at least one post-baseline ADA positive measurement and not fulfilling the conditions for TE-ADA persistently positive.
- nAb (to AZD7442) positive at any visit (at baseline and/or post-baseline).

17.1.2.2. ADA Analysis

A summary of the number and percentage of participants who developed detectable ADA to AZD7442 (ADA results to AZD8895 and AZD1061 will be reported separately) by ADA categories (Section 17.1.2.1) in different treatment arms will be presented based on the ADA evaluable analysis set. Descriptive statistics of the maximum

titer will also be presented by ADA category. ADA results and titers will be summarized by visit and treatment group. ADA results will be listed for all participants in the safety analysis set regardless of ADA-evaluable status. ADA titer and nAb data will be presented for samples confirmed positive for the presence of ADA to AZD7442. AEs in ADA positive participants by ADA positive category will be listed.

The effect of ADA on PK, safety, and efficacy will be examined by descriptive summaries if data permits.

17.1.3. AZD7442 NASAL FLUID CONCENTRATIONS

Individual AZD7442 (AZD8895 and AZD1061) nasal fluid concentration data will be listed and tabulated by mAb component, along with descriptive statistics for the participants in the PK analysis set who have at least one quantifiable nasal fluid PK observation post-dose.

17.1.4. NEUTRALIZING ANTIBODY GEOMETRIC MEAN TITERS AND GEOMETRIC MEAN FOLD RISE

Geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) for nAbs will be calculated for the active and control groups and will be summarized at each scheduled visit as per protocol section 1.3. GMT and GMFR summaries will be based on the nAb evaluable analysis set.

Descriptive statistics for GMTs and GMFRs will include number of participants, geometric mean, geometric standard deviation (GSD), 95% CI, minimum and maximum.

The GMT will be calculated as the antilogarithm of $\Sigma(\log_2$ transformed titer/n), i.e. as the antilogarithm transformation of the mean of the log-transformed titer, where n is the number of participants with titer information. The GSD for GMT will be calculated as the antilogarithm transformation of the standard deviation of the log-transformed titer. The 95% CI will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

The fold rise is calculated as the ratio of the post-dose titer level to the pre-dose titer level. GMFR will be calculated as anti-logarithm of Σ ($\log_2$ transformed (post-dose titer/ pre-dose titer)/n). The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT.

All nAb data will be listed.

17.1.5. MISSING DATA IMPUTATION METHOD FOR PK, PD, AND ADA ENDPOINTS

The PK descriptive analyses of serum AZD7442 concentrations (Section 17.1.1) and AZD7442 nasal fluid concentrations (Section 17.1.3) will use the following imputation methods: Individual concentrations below the LLOQ of the bioanalytical assay will be reported as Not Quantifiable (NQ) in the listings with the LLOQ defined in the footnotes of the relevant tables, figures, and listings (TFLs). Individual plasma concentrations that are Not Reportable (NR) will be reported as NR and those that are missing will be reported as No Sample (NS) in the listings. Plasma concentrations that are NQ, NR, or NS will be handled as follows for the provision of descriptive

statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the geometric mean, geometric mean ± GSD and geometric coefficient of variation (gCV%) will be set to Not Computed (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The geometric mean, minimum, median, and maximum will be reported as NQ and the gCV% and geometric mean ± GSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (e.g. Cmax, Cmin, Clast) to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

The analysis for the incidence of ADA to AZD7442 in serum (Section 17.1.2) will use the following imputation method: ADA titers values below the limit of detection (LOD) are negative results, hence they are not imputed and are excluded from calculation of summary statistics. Titer values of positive ADA samples reported as ≤ LOD are imputed as LOD in the calculation of summary statistics on ADA titer.

The analysis of neutralizing antibody geometric mean titers and geometric mean fold rise (Section 17.1.4) will use the following imputation method: a titer value measured below the LLOQ will be imputed to a value that is half of the LLOQ in summaries and analyses, but will be listed as reported in the raw data. Titer values measured as above the upper limit of quantification (ULOQ) will be imputed at the ULOQ value.

17.1.6. Sensitivity Analyses for PK, PD, and ADA Endpoints

No sensitivity analysis will be performed for the PK, PD, and ADA endpoints.

17.1.7. Supplementary Analyses for PK, PD, and ADA Endpoints

No supportive analysis will be performed for the PK, PD, and ADA endpoints.

18. Safety Endpoints

The safety of AZD7442 will primarily be assessed by:

- Incidence of AEs
- Incidence of SAEs
- Incidence of medically attended adverse events (MAAEs, defined in Protocol Section 8.3.5)
- Incidence of adverse events of special interest (AESIs, defined in Protocol Section 8.3.4)

There are also other safety endpoints, including:

- Deaths
- Laboratory evaluations
- Vital signs
- ECG evaluations
- Physical examinations

All safety summaries will be presented by actual treatment group based on the SAF and may be summarized by cohort and/or comorbidities. Additional summaries may be presented by whether participants receive COVID-19 vaccination or other COVID-19 preventive product (Yes/No) during study and unblinding status (Yes/No) during study. Data will be presented using all the available data up to 15 months (Day 457) following the dose of IMP to the last assessment unless stated otherwise. There will be no statistical comparisons between the treatment groups for safety data.

18.1. ADVERSE EVENTS

All AEs will be coded using the MedDRA dictionary, version 23.1 or higher.

Unless specified, event summary refers to the summary of number of participants with the corresponding adverse event.

Overall summaries of number and percentage of participants with AE in the following categories will be provided by treatment group based on the SAF.

- AEs
- SAEs
- Related SAEs
- AEs leading to IMP discontinuation
- Related AEs leading to IMP discontinuation
- AEs leading to study discontinuation

- Related AEs leading to study discontinuation
- MAAEs
- Related MAAEs
- AEs with outcome of death
- AESIs
- Related AESIs

Should a participant experience multiple events within a category, the participant will be counted only once for that category.

An overall summary of number and percentage of participants, including exposure adjusted rates, and number of events within categories of all SAEs, related SAEs, AEs leading to study discontinuation, related AEs leading to study discontinuation, MAAEs, AEs with outcome of death, and AESIs during the entire period of study will be provided by actual treatment group. Exposure adjusted rate is calculated as number of participants with AEs in categories above divided by total participant-year exposure to investigational study intervention. Participant years is determined by summing the total number of follow-up days of each participant, and then dividing by 365.25. The exposure period is calculated from time of dose to end of study.

An overall summary of number of AEs within each of the categories will also be provided by actual treatment group.

18.1.1. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs will be recorded from the time of IMP administration throughout the study up to and including the last visit. Serious adverse events (SAEs) are those events recorded as “Serious” on the AE page of the eCRF. SAEs will be recorded from the time of signing of the informed consent form.

Adverse events and serious adverse events post the dose of IMP will be summarized by SOC and PT by actual treatment group. Specific AEs will be counted once for each participant for calculating percentages.

Summary of AEs and SAEs post the dose of IMP will be broken down further by maximum severity and relationship to study intervention. If the same AE occurs multiple times for a particular participant, the highest/worst severity (i.e. from highest to lowest: severe, moderate and mild) and level of relationship to study intervention observed will be reported.

Listings of AEs and SAEs will be provided. SAEs prior to the dose of IMP and AEs and SAEs starting after Day 457 will only be presented in the listings. For SAEs with partial dates, if the known part of the date indicates that SAE stopped before the dose of IMP, it will be considered as SAE prior to the dose of IMP. Otherwise, it will be considered as SAE post dose of IMP.

18.1.1.1. Severity for AEs

Severity will be classified as mild, moderate, severe, potentially life-threatening, or fatal (increasing severity) by using grading for AEs. Severity for AEs will be collected on "Adverse Events" form of the eCRF. Should a participant experience multiple events within a SOC or PT, only the participant's worst severity grade will be counted for that SOC or PT.

18.1.1.2. Relationship to IMP/Other Medication/Study Procedure

Relationship to IMP/other medication/study procedure, as indicated by the Investigator, will be classified as not related or related.

Should a participant experience multiple events within a SOC or PT, the participant will be counted as related for that SOC or PT if one of those is related.

18.1.2. AEs Leading to Discontinuation of IMP

AEs leading to permanent discontinuation of IMP are not expected due to this being a single dose study. Given the single dose is comprised of 2 sequential injections, the AE would need to occur immediately after the 1st injection and lead to discontinuation of the 2nd injection—this scenario is expected to be rare. Therefore, no summary will be prepared.

A listing of all AEs leading to discontinuation of IMP will be provided, if data permit.

18.1.3. AEs Leading to Discontinuation of Study

A summary of AEs during the study leading to permanent discontinuation of study by SOC and PT will be prepared. A summary of related AEs leading to permanent discontinuation of study by SOC and PT will also be prepared.

A listing of all AEs leading to permanent discontinuation of study will be provided.

18.1.4. AEs with Outcome of Death

AEs with outcome of death are those AEs with "Fatal" outcome recorded on the "Adverse Events" form of the eCRF. A summary of AEs with outcome of death by SOC and PT will be prepared. A summary of related AEs with outcome of death by SOC and PT will also be prepared.

18.1.5. Medically Attended Adverse Events

Medically attended adverse events (MAAEs) are AEs leading to medically-attended visits that were not routine visits for physical examination or dosing, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine

study visit or during the scheduled Illness Visits will not be considered MAAEs. MAAEs will be recorded from Day 1, post dose, through the last participant contact.

A summary of MAAEs by SOC and PT by actual treatment group will be prepared. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT. A summary of related MAAEs by SOC and PT will also be prepared.

A listing of all MAAEs will be provided.

18.1.6. ADVERSE EVENTS OF SPECIAL INTEREST

AEs of special interest (AESIs) are:

- Anaphylaxis and other serious hypersensitivity reactions including immune complex disease
- Injection site reactions

AESIs are indicated on the eCRF and will be recorded from Day 1, post dose, through the last participant contact. A summary of AESIs by SOC and PT by actual treatment group will be prepared. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT. A summary of related AESIs by SOC and PT will also be prepared.

A listing of all AESIs will be provided.

18.2. DEATHS

If any participants die during the study as recorded on the "Death Details" page of the eCRF, the number and percentage of participants with death related to COVID-19 and those with other deaths will be summarized by actual treatment group based on the SAF. The number and percentage of participants with death related to COVID-19 as adjudicated by the MAC will also be summarized by actual treatment group based on the SAF.

A listing of all deaths will be provided.

18.3. LABORATORY EVALUATIONS

A urine pregnancy test will be performed at screening and per the schedule of events (refer to protocol, Section 1.3). If urine tests positive or indeterminate, a serum test will be performed for confirmation. Chemistry, hematology, coagulation, and urinalysis will be performed as per the schedule of events (refer to protocol, Section 1.3). A list of laboratory parameters to be included in the outputs is included in APPENDIX 3.

Quantitative laboratory parameters reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings

The following summaries will be provided by actual treatment group based on the SAF for each of chemistry, hematology, coagulation, and urinalysis laboratory parameter:

- Observed and change from baseline in Standard International (SI) units by visit (for quantitative parameters);
- Observed and change from baseline for Illness Visits as defined in Section 6.5 (for coagulation parameters) in SI units by Illness Visit (the Illness Visits corresponding to positive RT-PCR test will be used in the summary);
- Number and percentage of participants in each laboratory parameter category by visit (for categorical parameters);
- Shift from baseline to the worst post-baseline observed value according to the Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades (for quantitative parameters with available CTCAE toxicity grades; refer to Section 18.3.1)
- Shifts from baseline to the maximum/minimum post-baseline observed value according to normal range criteria (for quantitative parameters without CTCAE toxicity grades; refer to Section 18.3.2);
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-baseline total bilirubin (TBL) observed value categorized as < 2 x ULN or ≥ 2 x ULN

All laboratory evaluations will be listed.

18.3.1. CTCAE Toxicity Grades

Quantitative laboratory parameters with available CTCAE toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 4 for each parameter toxicity grade criteria):

- Grade 1 (i.e., mild);
- Grade 2 (i.e., moderate);
- Grade 3 (i.e., severe)
- Grade 4 (i.e., life-threatening)
- Grade 5 (i.e., death)

Although not defined in the CTCAE toxicity grading system, version 5, non-missing laboratory parameter results not meeting any of the 5 grades defined in the CTCAE toxicity grading system will be categorized as 'No Event' for the purpose of the shift from baseline summaries.

18.3.2. Laboratory Normal Ranges

Quantitative laboratory parameters will be compared with the relevant central laboratory normal ranges in SI units

and categorized as:

- Low: Below the lower limit of the laboratory normal range.
- Normal: Within the laboratory normal range (upper and lower limit included).
- High: Above the upper limit of the laboratory normal range.

18.4. VITAL SIGNS

The following vital sign parameters will be collected for this study as per the schedule of events (refer to protocol, Section 1.3):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Heart rate (beats per minute [bpm])
- Oxygen saturation (%)
- Respiratory rate (breaths/min)
- Body temperature (ºC)

For severity grades of abnormal Vital Signs refer to APPENDIX 5.

The following summaries will be provided by actual treatment group based on the SAF for each vital sign parameter:

- Observed and change from baseline by visit;
- Observed and change from baseline for Illness Visits (as defined in Section 6.5), by Illness Visit (the first illness episode with positive RT-PCR test result will be used for the summary);
- Number and percentages of participants with at least one abnormal post-baseline observed value (refer to APPENDIX 5);

All vital sign data will be listed. Indicators will be included for illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

18.5. ECG EVALUATIONS

The following electrocardiogram (ECG) parameters will be measured for this study as per the schedule of events (refer to protocol, Section 1.3):

- Heart rate (bpm);

- PR interval (msec);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTc interval (msec);
- QTcF interval (msec);
- QTcB interval (msec);
- Overall ECG interpretation (Investigator's judgment):
    - Normal;
    - Abnormal, not clinically significant (NCS);
    - Abnormal, clinically significant (CS)

Since triplicate ECGs will be performed for this study, the mean of the 3 measurements collected on a visit will be used in the by-visit summaries for that visit, but the worst of the 3 measurements collected on a visit will be used for the shift from baseline summaries for that visit. Should one or two of the triplicate measurements be missing at a specific visit, the mean of the available measurements will be used in the by-visit summaries for that visit. All individual measurements will be listed.

The following summaries will be provided by actual treatment group for each ECG parameter:

- Observed and change from baseline by visit (for quantitative parameters);
- Number and percentages of participants with at least one markedly abnormal post-baseline observed value/change from baseline (for quantitative parameters; refer to Section 18.5.1);

All ECG data will be listed.

18.5.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG parameters will be identified in accordance with the following predefined markedly abnormal criteria:

- Observed values for QTc, QTcF, and QTcB intervals will be classified as:
    - > 450 msec;
    - > 480 msec;

  - > 500 msec

- Change from baseline for QTc, QTcF, and QTcB intervals will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

It is to be noted that the previous categories are not mutually exclusive, but cumulative. For example, if a participant's worst post-baseline QTc post-baseline observed value is 490 mmHg, then this participant will be reported once under QTc > 450 msec and once under QTc > 480 msec.

18.6. PHYSICAL EXAMINATION

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 1.3). Clinically significant findings at screening will be recorded on the "Medical History" form of the eCRF while clinically significant changes from screening will be recorded on the "Adverse Events" form of the eCRF for the post-screening visits. Hence, clinically significant findings/changes will be summarized through the Medical history summary (refer to Section 11) or AE summaries (refer to Section 18.1), as appropriate. That is, no summaries will be specifically provided for the general physical examination.

19. OTHER DATA COLLECTED

The following data collected on the eCRF will be summarized in listings only:

- Exposure
- Pregnancy test and report
- Overdose Report
- Medication Error
- Virology: Hepatitis B surface antigen, hepatitis C virus antibody; HIV-I and HIV-II
- Rapid point of care SARS-CoV-2 serology
- Related procedures
- PBMCs for B and T cell responses
- Nasal adsorption for SARS-CoV-2 mucosal responses
- Pharmacogenetics

20. REFERENCES

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APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known or ongoing	If medication stop date < date of dose of IMP, assign as prior; If medication start date < date of dose of IMP and medication stop date ≥ date of dose of IMP, assign as concomitant; If date of dose of IMP ≤ medication start date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of dose of IMP, assign as prior; If medication start date < date of dose of IMP and (known components of medication stop date show that medication stopped on or after date of dose of IMP), assign as concomitant; If date of dose of IMP ≤ medication start date, assign as concomitant.
	Missing, not ongoing	If medication stop date is missing, then it can never be assigned as prior only; If medication start date < date of dose of IMP, assign as concomitant; If date of dose of IMP ≤ medication start date, assign as concomitant.
Partial	Known or ongoing	If medication stop date < date of dose of IMP, assign as prior; If (known components of medication start date show that medication started before date of dose of IMP) and (medication stop date ≥ date of dose of IMP), assign as concomitant; If known components of medication start date show that medication started on or after date of dose of IMP, assign as concomitant.

START DATE	STOP DATE	ACTION
	Partial	If known components of medication stop date show that medication stopped before date of dose of IMP, assign as prior; If (known components of medication start date show that medication started before date of dose of IMP) and (known components of medication stop date show that medication stopped on or after date of dose of IMP), assign as concomitant; If known components of medication start date show that medication started on or after date of dose of IMP, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before study drug start date, assign as concomitant; If known components of medication start date show that medication started on or after date of dose of IMP, assign as concomitant.
Missing	Known or ongoing	If medication stop date < date of dose of IMP, assign as prior; If medication stop date >= date of dose of IMP, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of dose of IMP, assign as prior; If known components of medication stop date show that medication stopped on or after date of dose of IMP, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm:ss.

SPELLING FORMAT

English US.

PAPER SIZE, ORIENTATION, AND MARGINS

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

FONTS

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	Tables and Graphs	Listings
AZD7442	1	1
Placebo	2	2
Total [1]	5	n/a
Randomized, Not Dosed	n/a	3
Screen Failure	n/a	4

[1] Not applicable for efficacy tables, safety tables and graphs.

PK analyses will be conducted for participants who receive AZD7442 only. Groups will be represented as follows and in the given order:

Treatment Group	Tables and Graphs	Listings
AZD8895	1	1
AZD1061	2	2
AZD7442	3	3

PRESENTATION OF NOMINAL VISITS

For outputs, analysis visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scrn
Rescreening	RScrn
Day 1	D1
Day 8	D8
Day 29	D29
Day 58	D58
Day 92	D92
Day 183	D183
Day 366	D366
Day 457	D457

For outputs, analysis visits regarding Illness Visit will be represented as follows and in that order:

Long Name (default)	Short Name
Episode 1 Illness Visit Day X, X=1,3,5,8,11,14,21,28	1IL-DXX, X=1,3,5,8,11,14,21,28
Episode 2 Illness Visit Day X,	2IL-DXX,

Long Name (default)	Short Name
X=1,3,5,8,11,14,21,28	X=1,3,5,8,11,14,21,28
Episode Y Illness Visit Day X, X=1,3,5,8,11,14,21,28 Y = 1, 2, 3, and so on, as applicable	YIL-DXX, X=1,3,5,8,11,14,21,28 Y = 1, 2, 3, …

DESCRIPTIVE STATISTICS

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, Q1, Q3, lower and upper bounds of two-sided 95% CI: N + 1;
- SD and SE: N + 2

PERCENTAGES

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

P-VALUES

p-values will be reported to four decimal places. Rounding will be applied, except for the p-values < 0.0001 which will be presented as '< 0.0001' and p-values < 1.000 but > 0.9999 which will be presented as '> 0.9999'.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Randomized treatment group (or treatment received if it's a safety output);
- Participant ID;
- Parameter, when applicable;
- Date/Time, when applicable;
- Timepoint, when applicable

APPENDIX 3. LABORATORY ASSESSMENTS

Chemistry (SI unit)	
• Alkaline phosphatase (ALP) (U/L)	• Creatinine (µmol/L)
• Alanine transaminase (ALT) (U/L)	• Glucose (mmol/L)
• Aspartate transaminase (AST) (U/L)	• Creatine kinase (CK) (U/L)
• Total bilirubin (µmol/L)	• Sodium (mmol/L)
• Conjugated bilirubin (µmol/L)	• Potassium (mmol/L)
• Gamma glutamyl transferase (GGT) (U/L)	• Calcium (mmol/L)
• C-Reactive protein (CRP) (nmol/L)	• Phosphate (mmol/L)
• Albumin (g/L)	• Urea (mmol/L)

Hematology (SI unit)	
• Hemoglobin (g/L)	• Absolute neutrophils count (x10E9/L)
• Hematocrit	• Absolute lymphocyte count (x10E9/L)
• Mean corpuscular volume (MCV) (fL)	• Absolute monocyte count (x10E9/L)
• Red blood cells (RBC) count total (x10E12/L)	• Absolute eosinophils count (x10E9/L)
• White blood cell (WBC) count total (x10E9/L)	• Absolute basophils count (x10E9/L)
• Mean corpuscular hemoglobin (MCH) (pg)	• Absolute reticulocyte count (x10E9/L)
• Mean corpuscular hemoglobin concentration (MCHC) (g/L)	• Platelet count (x10E9/L)

Coagulation (SI unit)

- International normalized ratio (INR)
- Activated partial thrombin time (aPTT) (s)
- Prothrombin time (PT) (s)

Urinalysis (SI unit)

Dip stick

- Blood
- Protein
- Glucose

Microscopy

- White blood cells
- Red blood cells
- Casts

APPENDIX 4. CTCAE TOXICITY GRADE, VERSION 5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed on 22-Apr-2020)

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (g/L)	≥ LLN	≥ 100 g/L - < LLN	≥ 80 - < 100 g/L	< 80 g/L	n/a	n/a
Hemoglobin increased	Hemoglobin (g/L)	No increase from baseline	Increase from baseline > 0 - ≤ 20 g/L	Increase from baseline > 20 - ≤ 40 g/L	Increase from baseline > 40 g/L	n/a	n/a
Platelet count decreased	Platelet count (x10E9/L)	≥ LLN	≥ 75 x 10E9/L – < LLN	≥ 50 - < 75 x 10E9/L	≥ 25 - < 50 x 10E9/L	< 25 x 10E9/L	n/a
White blood cell (WBC) decreased	WBC (x 10E9/L)	≥ LLN	≥ 3.0 x 10E9/L – < LLN	≥ 2.0 - < 3.0 x 10E9/L	≥ 1.0 - < 2.0 x 10E9/L	< 1.0 x 10E9/L	n/a
Leukocytosis	WBC (x 10E9/L)	≤ 100 x 10E9/L	n/a	n/a	> 100 x 10E9/L	n/a	n/a
Absolute neutrophils count decreased	Absolute neutrophils count (x 10E9/L)	≥ LLN	≥ 1.5 x 10E9/L – < LLN	≥ 1.0 - < 1.5 x 10E9/L	≥ 0.5 - < 1.0 x 10E9/L	< 0.5 x 10E9/L	n/a
Absolute lymphocytes count decreased	Absolute lymphocytes count (x 10E9/L)	≥ LLN	≥ 0.8 x 10E9/L – < LLN	≥ 0.5 - < 0.8 x 10E9/L	≥ 0.2 - < 0.5 x 10E9/L	< 0.2 x 10E9/L	n/a
Absolute lymphocytes count increased	Absolute lymphocytes count (x 10E9/L)	≤ 4 x 10E9/L	n/a	> 4 – ≤ 20 x 10E9/L	> 20 x 10E9/L	n/a	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eosinophilia	Absolute eosinophils	≤ ULN or ≤ Baseline	> ULN and > Baseline	n/a	n/a	n/a	n/a
Hypernatremia	Sodium (mmol/L)	≤ ULN	> ULN – ≤ 150 mmol/L	> 150 – ≤ 155 mmol/L	> 155 – ≤ 160 mmol/L	> 160 mmol/L	n/a
Hyponatremia	Sodium (mmol/L)	≥ LLN	≥ 130 mmol/L – < LLN	≥ 125 - < 130 mmol/L	≥ 120 - < 125 mmol/L	< 120 mmol/L	n/a
Hyperkalemia	Potassium (mmol/L)	≤ ULN	> ULN – ≤ 5.5 mmol/L	> 5.5 – ≤ 6.0 mmol/L	> 6.0 – ≤ 7.0 mmol/L	> 7.0 mmol/L	n/a
Hypokalemia	Potassium (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	n/a	≥ 2.5 - < 3.0 mmol/L	< 2.5 mmol/L	n/a
Hypercalcemia	Ionized calcium (mmol/L)	≤ ULN	> ULN – ≤ 1.5 mmol/L	> 1.5 – ≤ 1.6 mmol/L	> 1.6 – ≤ 1.8 mmol/L	> 1.8 mmol/L	n/a
Hypocalcemia	Ionized calcium (mmol/L)	≥ LLN	≥ 1.0 mmol/L – < LLN	≥ 0.9 - < 1.0 mmol/L	≥ 0.8 - < 0.9 mmol/L	< 0.8 mmol/L	n/a
Hypermagnesemia	Magnesium (mmol/L)	≤ ULN	> ULN – ≤ 1.23 mmol/L	n/a	> 1.23 – ≤ 3.30 mmol/L	> 3.30 mmol/L	n/a
Hypomagnesemia	Magnesium (mmol/L)	≥ LLN	≥ 0.5 mmol/L – < LLN	≥ 0.4 - < 0.5 mmol/L	≥ 0.3 - < 0.4 mmol/L	< 0.3 mmol/L	n/a
Hypoglycemia	Glucose (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	≥ 2.2 - < 3.0 mmol/L	≥ 1.7 - < 2.2 mmol/L	< 1.7 mmol/L	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	Creatinine (µmol/L)	≤ ULN	> ULN – ≤ 1.5 x ULN	> 1.5 – ≤ 3.0 x ULN **or** > 1.5 – ≤3.0 x baseline	> 3.0 – ≤ 6.0 x ULN **or** > 3.0 x baseline	> 6.0 x ULN	n/a
Alkaline phosphatase (ALP) increased	ALP (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5 x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Alanine transaminase (ALT) increased	ALT (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate transaminase (AST) increased	AST (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Blood bilirubin increased	Total bilirubin (µmol/L)	≤ ULN if baseline normal; ≤ baseline if baseline abnormal	> ULN – ≤ 1.5 x ULN if baseline normal; > baseline - ≤ 1.5 x baseline if baseline abnormal	> 1.5 – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 10.0 x ULN if baseline normal; > 3.0 - ≤ 10.0 x baseline if baseline abnormal	> 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal	n/a
Gamma glutamyl transferase (GGT) increased	GGT (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 - ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 - ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoalbuminemia	Albumin (g/L)	≥ LLN	≥ 30 g/L - < LLN	≥ 20 - < 30 g/L	< 20 g/L	n/a	n/a
CPK increased	Creatine kinase (U/L)	≤ ULN	> ULN – ≤ 2.5 x ULN	> 2.5 – ≤ 5 x ULN	> 5 – ≤ 10 x ULN	> 10 x ULN	n/a
International normalized ratio (INR) increased	INR	≤ 1.2 if not on anticoagulant; ≤ baseline if on anticoagulant	> 1.2 – ≤1.5 if not on anticoagulant; > baseline - ≤ 1.5 x baseline if on anticoagulant	> 1.5 – ≤2.5 if not on anticoagulant; > 1.5 - ≤ 2.5 x baseline if on anticoagulant	> 2.5 if not on anticoagulant; > 2.5 x baseline if on anticoagulant	n/a	n/a

APPENDIX 5. CLINICAL ABNORMALITIES: VITAL SIGNS

Vital Signs [a]	Vital Signs Grade			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) [b] (°F) [b]	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia (beats/minute)	101-115	116- 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats/minute) [c]	50-54	45-49	< 45	ER visit or hospitalization for arrhythmia
Hypertension; systolic (mm Hg)	141-150	151-155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension; diastolic (mm Hg)	91-95	96-100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension; systolic (mm Hg)	85-89	80-84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	> 25	Intubation

Note: Record vital signs as adverse events only if clinically relevant and changed from baseline.

[a] Participant should be at rest for vital signs measurements.

[a] No recent hot or cold beverages or smoking.

[b] Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

ER = emergency room; Hg = mercury.

APPENDIX 6. HIGH RISK OF SEVERE COVID-19 AT BASELINE

High Risk of Severe COVID-19 Condition	Description
History of Obesity: (eCRF)	COVID Co-Morbidities eCRF: "Does the subject have a history of Obesity -- those with a BMI greater than 30" Programming example: MHDIAGYN4 = "Y"
Obese: BMI ≥30 (derived)	Derived from the participant's reported height and weight at baseline
Morbid Obesity: BMI ≥40 (derived)	Derived from the participant's reported height and weight at baseline
CKD	COVID Co-Morbidities eCRF: "Does the subject have a history of Chronic kidney disease?" Programming example: MHDIAGYN1 = "Y"
Diabetes	COVID Co-Morbidities eCRF: "Does the subject have a history of Type 1 diabetes?" "Does the subject have a history of Type 2 diabetes?" Programming example: MHDIAGYN15 = "Y" or MHDIAGYN7 = "Y"
Immunosuppressive disease	From reported Medical History Term Programming example: SOC_NAME = "IMMUNE SYSTEM DISORDERS" and HLGT different than 'ALLERGIC CONDITIONS'
Immunosuppressive treatment	From reported Concomitant medications identified as prior and ongoing with ATC2 is 'L01' or 'L04'.
CV disease	COVID Co-Morbidities eCRF: "Does the subject have a history of Serious heart conditions like heart failure and coronary artery disease" Programming example: MHDIAGYN5 = "Y"
COPD	COVID Co-Morbidities eCRF: "Does the subject have a history of Chronic obstructive pulmonary disease (COPD), like emphysema?" Programming example: MHDIAGYN2 = "Y"
Chronic liver disease	COVID Co-Morbidities eCRF: "Does the subject have a history of Liver disease?" Programming example: MHDIAGYN13 = "Y"
Hypertension	COVID Co-Morbidities eCRF: "Does the subject have a history of High blood pressure?" Programming example: MHDIAGYN12 = "Y"
Asthma	COVID Co-Morbidities eCRF: "Does the subject have a history of Asthma?" Programming example: MHDIAGYN8 = "Y"
Cancer	From ongoing Medical History terms where SOC NAME='NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)' and PT name different than 'UTERINE LEIOMYOMA'
Smoking	COVID Co-Morbidities eCRF: "What is the subject's smoking history?" MHDIAGYN17 = "1" ("Current smoker")

High Risk of Severe COVID-19 Condition	**Description**
Sickle cell disease	COVID Co-Morbidities eCRF: "Does the subject have a history of Sickle cell disease?" Programming example: MHDIAGYN6 = "Y"

Note: Final programming logic may differ to address the specific data elements such as additional fields, different field name, or levels.

APPENDIX 7. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Class
AUC	area under the plasma concentration-time curve
BMI	body mass index
BLQ	below the lower limit of quantification
BSSR	blinded sample size re-estimation
CI	confidence interval
COVID-19	coronavirus disease 2019
CDC	Centers for Disease Control and Prevention
CMH	Cochran-Mantel-Haenszel
CS	clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DBP	diastolic blood pressure
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FAS	full analysis set
FPAS	full pre-exposure analysis set
gCV%	geometric coefficient of variation
GMT	geometric mean titers
GMFR	geometric mean fold rise
GSD	geometric standard deviation
IA	interim analysis
IM	intramuscular
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology

Abbreviation or special term	Explanation
ITT	intent-to-treat
LLOQ	lower limit of quantification
LOD	limit of detection
MAAE	medically attended adverse event
mAbs	monoclonal antibodies
MAC	Morbidity Adjudication Committee
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
NCS	not clinically significant
NP	nasopharyngeal
NQ	not quantifiable
NR	not reportable
NS	no sample
PAS	all participants analysis set
PD	pharmacodynamic
PH	proportional hazard
PK	pharmacokinetic(s)
PT	preferred term
RR	relative risk
RRR	relative risk reduction
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SI	Standard International
SOC	system organ class
TBL	total bilirubin level
TE-ADA	treatment-emergent ADA
TFLs	tables, figures, and listings
TMA	Therapeutic Medical Advisor
ULN	upper limit of normal
ULOQ	upper limit of quantification

Abbreviation or special term	Explanation
ULQ	above the upper limit of quantification
WHO	World Health Organization

SIGNATURE PAGE

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